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DRUG EVALUATION IN THE

PLASMODIUM FALCIPARUM - AOTUS MODEL

FINAL REPORT

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Aotus trivirgatus	8-aminoquinoline	2-fluoro-l-histidine
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		desferrioxamine

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Infections in Aotus trivirgatus of two strains of Plasmodium falciparum, Uganda Palo Alto (chloroquine-sensitive) or Vietnam Smith (chloroquine-resistant), or the New Guinea-Chesson strain of P. vivax, were used to assess the blood schizonticidal/curative activity of experimental antimalarial drugs. WR 245082, an acridineamine, at similar doses cured infections of chloroquine-sensitive and-resistant P. falciparum strains. Each of three 8-aminoquinolines, at doses of 1.0 or 4.0 mg base per kg (x 3 days), cured trophozoite-induced infections of P. vivax. A quinoline, WR 247705, cured Uganda Palo Alto

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19. 9-phenanthrenemethanol
sodium artesunate

20. strain infections. WR 251853, 2-fluoro-l-histidine, administered as single or multiple intravenous doses, was ineffective against Uganda Palo Alto parasitemias. A single intravenous dose or three oral doses of 2-iodo-histidine had no effect upon Uganda Palo Alto infections. Desferrioxamine (WR 079520), administered via osmotic pump, suppressed Uganda Palo Alto parasitemias. Injection of desferrioxamine plus osmotic pump only cleared parasitemia. WR 250547, an acridinol, cured blood-induced infections of P. vivax. When two stereoisomers of floxacrine, WR 250547 and WR 250548, were administered in combination against Vietnam Smith infections a potentiating antimalarial effect was observed. Of three 9-phenanethrene methanols assessed, both the chloride and biquinate salt of halofantrine (WR 171669) were not effective against Vietnam Smith infections; WR 122455 cured all previous treatment failures and also primary infections. Sodium artesunate, a derivative of Qinghaosu, suppressed an Uganda Palo Alto parasitemia. Trials were begun to adapt the UNC-W2-MEF clone of the CDS Indochina III strain of P. falciparum to Aotus.

SUMMARY

The experimental antimalarial drug studies summarized herein are for the period 1 August 1984 - 31 October 1986. The model used for these evaluations was the Panamanian Aotus trivigatus infected with trophozoites of either Plasmodium falciparum (Uganda Palo Alto or Vietnam Smith strain) or P. vivax (New Guinea - Chesson strain).

The curative activity of WR 245082, an acridineamine, for chloroquine-sensitive and chloroquine-resistant strains of P. falciparum was similar. Infection cures in 50% of the monkeys were obtained with a dose of 1.0 mg base per kg (x 3 days), and a dose of 4.0 or 16.0 mg base per kg (x 3 days) cured 100% of the infections.

Three 8-aminoquinolines were evaluated for their activity against blood-induced infections of P. vivax. WR 249420, at a dose of 1.0 mg base per kg (x 3 days), cured such infections. Both WR 249252 and WR 249700 were curative each at a dose of 4.0 mg base per kg (x 3 days).

A quinoline, WR 247705, was assessed for its activity against infections of the Uganda Palo Alto strain of P. falciparum. A dose of 4.0 mg base per kg (x 3 days) cured 50% of the infections, and a dose of 16.0 mg base per kg (x 3 days) cured 75% of the infections.

The antimalarial activity of two analogues of the amino acid histidine was assessed against infections of the Uganda Palo Alto strain. WR 251853, 2-fluoro-l-histidine, administered intravenously at a dose of 25.0 mg base per kg (x 7 days) suppressed parasitemia in 1 of 2 Aotus. Parasitemia was suppressed by a 50.0 mg base per kg dose in each of 2 Aotus but both animals died on day 6 of treatment of drug toxicity. A single intravenous dose of 50.0 or 100.0 mg base per kg of 2-fluoro-l-histidine had no effect upon parasitemias.

The 2-iodo-histidine analogue, administered as a single intravenous dose of 200.0 or 400.0 mg base per kg, had no activity against Uganda Palo Alto infections. Oral retreatment with a total of three 100.0 mg base per kg doses of 2-iodo-histidine showed no activity against these infections.

An iron-specific chelating agent, desferrioxamine (WR 079520), was administered to Aotus infected with the Uganda Palo Alto strain of P. falciparum either by subcutaneous implantation of osmotic pumps or subcutaneous injection. When WR 079520 was delivered by osmotic pump(s) only, parasitemia was suppressed in 6 of 7 Aotus. Subcutaneous injection of desferrioxamine had no effect upon parasitemia, but when administered in combination with an osmotic pump implant, the parasitemia was cleared in 1 of 2 Aotus; however, the infection was not cured.

WR 250547, an acridinol when administered at doses of 4.0 or 16.0 mg base per kg (x 3 days) cured blood-induced infections of P. vivax.

Previous evaluation of two stereoisomers of floxacrine showed that WR 250547, at doses of 1.0, 4.0, or 16.0 mg base per kg (x 3 days), cured infections of the

multi-drug resistant Vietnam Smith strain. WR 250548 did not clear and/or cure Vietnam Smith infections when administered at similar doses. When both drugs were given in combination, a potentiating antimalarial effect against Vietnam Smith infections was observed. WR 250547 plus WR 250548, each administered at a dose of 0.5 or 1.0 mg base per kg (x 3 days) cleared and/or cured Vietnam Smith infections. Other dose ratios of 0.5 and 2.0, 2.0 and 0.5, 1.0 and 4.0, and 4.0 and 1.0, were equally effective in curing Vietnam Smith infections.

The antimalarial activities of three 9-phenanethrenemethanols were assessed against infections of the Vietnam Smith strain. At dosesof 2.9, 5.8, or 11.7 mg base per kg (x 3 days), the chloride salt of halofantrine was not effective against primary parasitemias and cured two infections in a total of 22 treatments. The biquinate salt of halofantrine, WR 171669AP, did not clear primary parasitemias when administered at doses of 2.9, 5.8, or 11.7 mg base per kg (x 3 days) and after retreatments cured one of 21 infections. WR 122455 at a dose of 5.8 or 11.7 mg base per kg (x 3 days) cured 3 of 4 primary Vietnam Smith infections, and all recrudescences following treatment with either WR 171669AM or WR 171669AP.

Pilot evaluation of sodium artesunate, a derivative of Qinghaosu, showed that intravenous administration of a 30.0 mg per kg (x 2 days) dose temporarily suppressed Uganda Palo Alto parasitemia in one Aotus.

Trials were initiated to adapt the UNC-W2-MEF clone of the CDS Indochina III strain of P. falciparum to Aotus. To date, parasitemias greater than 1,000 per mm^3 have been obtained only in a splenectomized Aotus of Colombian origin.

FOREWORD

In conducting the research described in this report, the investigators adhered to the "Guide for the Care and Use of Laboratory Animals," prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council (DHEW Publication No. (NIH) 78-23, Revised 1978).

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INTRODUCTION

This is the Final Report for Army Contract DAMD 17-84-C-4215, "Drug Evaluation in the *Plasmodium falciparum* - *Aotus* Model" for the period 1 August 1984 - 31 October 1986. Annual Reports, detailing the results of evaluations of experimental antimalarial drugs, have been submitted. This report is a summary of the two Annual Reports.

EXPERIMENTAL PROCEDURES

Two monkey-adapted Plasmodium falciparum strains, Vietnam Smith (resistant to maximally tolerated doses of chloroquine, pyrimethamine, and quinine), and Uganda Palo Alto (sensitive to chloroquine and quinine, resistant to pyrimethamine) were used to induce experimental malaria infections in Aotus trivirgatus for the evaluation of the antimalarial efficacy of candidate drugs. Additionally, infections of P. vivax, Chesson (sensitive to chloroquine, pyrimethamine, and quinine) constituted a test system for some of the drugs. Infected blood, with sodium citrate (2.5) as the anticoagulant, from untreated Aotus was diluted appropriately with chilled saline (0.85), such that each milliliter contained 5,000,000 parasites, and this amount was injected into the saphenous vein of experimental and control monkeys.

Blood films, prepared and examined daily beginning on the first post-inoculation day, were stained with Giemsa. Parasitemias were evaluated as follows: negative, if no parasites were detected on a thick blood film after examination for at least 5 minutes; <10 parasites per cmm, if positive only on thick blood film; parasite enumeration was by the Earle-Perez method and reported as the number of parasites per cmm.

Blood films from untreated Aotus, serving as passage and/or control subjects, were prepared and examined daily during the primary patent period, and daily thereafter for at least three consecutive days after parasites could last be detected on thick blood films. When parasitemia had cleared, films were made and examined twice weekly until a total of 100 negative days had been recorded. If a recrudescence occurred, blood films were obtained again on a daily basis.

The schema depicted in Figure 1 represents the design of a typical drug evaluation study. Parasitemias were evaluated daily (or twice daily) during the treatment period and until blood films were negative for at least seven consecutive days. The frequency of smearing was then reduced to two times per week (Monday and Thursdays or Tuesdays and Fridays). If no recrudescences occurred during a 100 day examination period, the infection was considered to have been cured.

Drug doses were calculated as mg base per kg of body weight. Stock solution of water soluble compounds, at appropriate concentrations, were prepared with distilled water and stored at 3°C for the treatment period. If a compound was water insoluble, a suspension of the requisite amount of drug was prepared daily with 0.3 methylcellulose (in distilled water).

Oral administration of drugs was effected by gastric intubation with a 14 French catheter. The total amount of fluid administered, drug solution or suspension, and rinse was 14 ml.

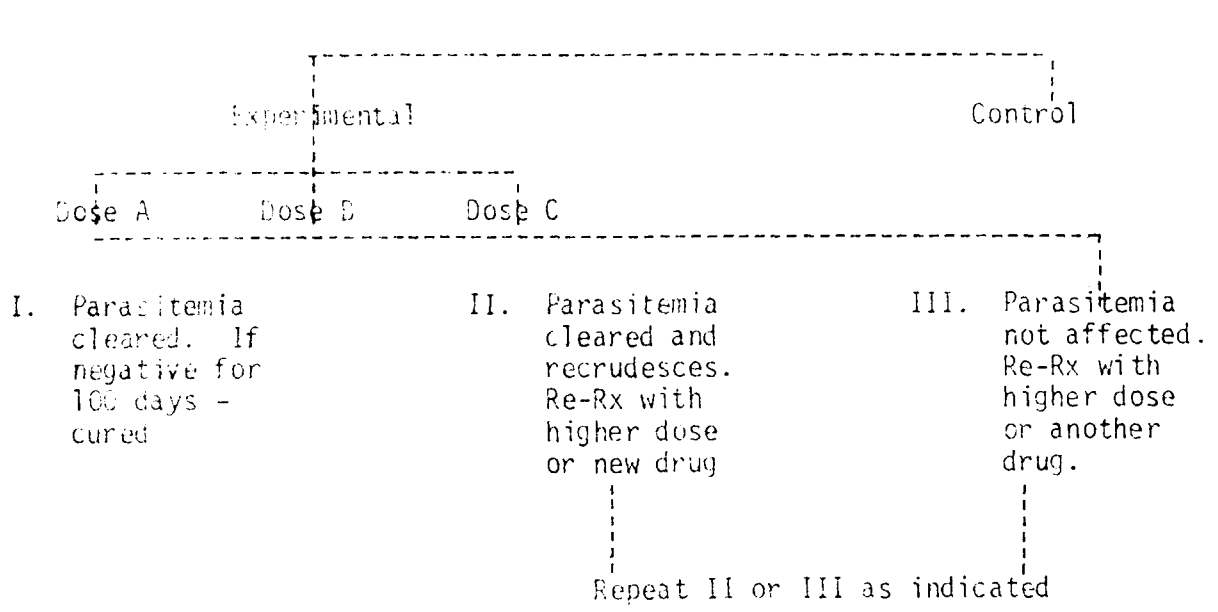
As will be indicated in subsequent sections, some drugs were administered other than by gastric intubation. In such instances, the route of drug administration was either intravenous, subcutaneous, or by implantation (subcutaneous) of one or more osmotic pumps.

FIGURE 1

SCHEMA FOR DRUG EVALUATION AGAINST

PLASMODIUM FALCIPARUM AND *P. VIVAX* TROPHOZOITE -

INDUCED INFECTIONS IN *AOTUS TRIVIRGATUS*



ASSESSMENT OF THE ACTIVITY OF WR 245082AA (BN: BJ 28403) AGAINST INFECTIONS OF THE UGANDA PALO ALTO AND VIETNAM SMITH STRAINS OF PLASMODIUM FALCIPARUM

When evaluated against infections of the chloroquine-sensitive Uganda Palo Alto strain, this acridineimine at a dose of 1.0 mg base per kg (x 3 days) cured 1 of 2 primary infections. A dose of 4.0 mg base per kg (x 3 days) cured 2 of 2 primary infections and 1 of 1 recrudescent infection; WR 245082 at a dose of 16.0 mg base per kg (x 3 days) cured 2 of 2 primary infections.

Parasitemias of the chloroquine-resistant Vietnam Smith strain were not affected by primary treatment with doses of either 0.0625 or 0.25 mg base per kg (x 3 days), nor by repeat treatment with the latter dose. A dose of 1.0 mg base per kg (x 3 days) cured 2 of 4 primary infections and a dose of 4.0 mg base per kg (x 3 days) cured 2 of 2 primary and 3 of 5 recrudescent infections. When administered at a dose of 16.0 mg base per kg (x 3 days), 2 of 2 primary and 2 of 2 recrudescent infections were cured.

The curative activity of WR 245082 against primary infections of chloroquine-sensitive and chloroquine-resistant strains was virtually the same, 50% of infections were cured with a dose of 1.0 mg base per kg (x 3 days), and all infections were cured with a dose of either 4.0 or 16.0 mg base per kg (x 3 days).

ASSESSMENT OF THE ANTIMALARIAL ACTIVITY OF THREE 8-AMINOQUINOLINES AGAINST BLOOD-INDUCED INFECTIONS OF THE NEW GUINEA-CHESSON STRAIN OF PLASMODIUM VIVAX

A. WR 249420AB (BN: BK 56537)

Although a dose of 0.25 mg base per kg (x 3 days) had no activity against the trophozoites in 2 of 2 Aotus infected with the Chesson strain of P. vivax, retreatment with a dose of 1.0 mg base per kg (x 3 days) cured infection in both monkeys and this dose cured a primary infection in 1 of 2 Aotus. A dose of 4.0 or 16.0 mg base per kg (x 3 days) cured all primary and recrudescent infections.

B. WR 249252AA (BN: BJ 76365)

This 8-aminoquinoline, administered at a dose of 1.0 mg base per kg (x 3 days) was ineffective primary parasitemias of P. vivax. Primary treatment with a dose of 4.0 mg base per kg (x 3 days) cured 1 of 2 infections and repeat treatment with this dose cured 1 of 2 infections. One of 2 primary infections and 2 of 2 recrudescences were cured with a dose of 16.0 mg base per kg (x 3 days), while a dose of 64.0 mg base per kg (x 3 days) cured 1 of 1 recrudescent infection.

C. WR 249700AA (BN: BK 01676)

When administered at a dose of 1.0 mg base per kg (x 3 days), this drug had no effect upon parasitemia in 2 of 2 monkeys. Retreatment with a dose of 4.0 mg base per kg (x 3 days) cured infections in both Aotus, and also cured 1 of 2 primary infections. A dose of 16.0 mg base per kg (x 3 days) cured 1 of 2 primary infections and 1 of 1 recrudescent infections. A retreatment with a dose 64.0 mg base per kg (x 3 days) cured a treatment failure.

At the present time primaquine is the only drug available for the radical cure of sporozoite-induced infections of P. vivax. This 8-aminoquinoline, however, is essentially inactive against the trophozoite stages of P. vivax. A long-sought goal is to identify a drug that is active against both P. vivax trophozoites and the forms responsible for initiating relapse. WR 249420 cured trophozoite -induced infections when administered at a dose of 1.0 mg base per kg (x 3 days), and 249252 and WR 249700 cured such infections when each were administered at a dose of 4.0 mg base per kg (x 3 days). The radical curative activity of these drugs has not been evaluated in Aotus.

ASSESSMENT OF THE ACTIVITY OF WR 247705AB (BN: BK 57098) AGAINST INFECTIONS OF THE UGANDA PALO ALTO STRAIN OF PLASMODIUM FALCIPARUM

Primary parasitemias of the chloroquine-sensitive Uganda Palo Alto strain were not cleared with this quinoline when administered at a dose of 1.0 mg base per kg (x 3 days). Retreatment with a dose of 4.0 mg base per kg (x 3 days) cured these infections, and this dose cleared 2 of 2 primary parasitemias. A dose of 16.0 mg base per kg (x 3 days) cured of 1 of 2 primary infections, and 2 of 2 recrudescent infections. Retreatment with a dose 64.0 mg base per kg (x 3 days) cured the infection in the one Aotus so treated.

Results of a previous evaluation with this quinoline against infections of the chloroquine-resistant Vietnam Smith strain indicated that cures were obtained in 25% of the monkeys treated with a dose of 4.0 mg base per kg (x 3 days) and 100% of the infections were cured by a dose of 16.0 mg base per kg (x 3 days). When the drug was evaluated against infections of the chloroquine-sensitive Uganda Palo Alto strain, 50% of the infections were cured by a 4.0 mg base per kg (x 3 days) dose, and a dose of 16.0 mg base per kg (x 3 days) cured 75% of the infections. The activity of WR 247705 appeared not to be compromised by chloroquine resistant plasmodia.

ASSESSMENT OF THE ANTIMALARIAL ACTIVITY OF WR 251853AA (BN: BK 70877), 2-FLUORO L-HISTIDINE, AND 2-IODO-HISTIDINE AGAINST INFECTIONS OF THE UGANDA PALO ALTO STRAIN OF PLASMODIUM FALCIPARUM

In vitro studies with the Malayan Camp strain of P. falciparum at the Malaria Laboratory, N. I. A. I. D., N. I. H., Bethesda, Md. indicated that the 2-fluoroanalogue of the amino acid histidine inhibited parasite growth, and inhibited knob formation of parasitized erythrocytes. In vivo knob formation of falciparum - infected erythrocytes is responsible for deep-vascular sequestration which partly allows the parasites to escape the immune mechanism.

A pilot evaluation of 2-fluoro-l-histidine administered intravenously to Aotus infected with the Uganda Palo Alto strain of P. falciparum showed that a total daily dose of 25.0 mg base per kg (x 7 days) suppressed the parasitemia in of 1 of 2 monkeys. The parasitemia in 2 of 2 Aotus was suppressed by a total daily dose of 50.0 mg base per kg (x 5 days). Both monkeys died on day 6, after initiation of treatment, with pathology attributable to drug toxicity.

Despite the in vivo toxicity of 2-fluoro-l-histidine at the regimens used, it was considered that the significant in vitro activity of WR 251853 warranted additional antimalarial trials in Aotus. In a cooperative effort, Dr. Lindsey Panton, Malaria Laboratory, N.I.H., spent one month at Gorgas Memorial Laboratory, assisting in a re-evaluation of 2-fluoro-l-histidine, as well as another histidine analogue, 2-iodo-histidine.

For the re-evaluation against Uganda Palo Alto infections, 2 fluoro-l-histidine was administered as a single intravenous dose at 50.0 mg base per kg. The parasitemia in each of two monkeys was not affected. A single 100.0 mg base per kg intravenous dose suppressed the parasitemia in one Aotus, and had no effect upon the parasitemia in another Aotus. While no drug toxicity was observed at these regimens, neither was any antimalarial activity.

Single intravenous doses of 2-iodo-histidine were evaluated against Uganda Palo Alto infections - neither 200.0 or 400.0 mg base per kg was effective against parasitemias in a total of four Aotus. All monkeys were re-treated orally with a 100.0 mg base per kg dose administered once on Day 1 of treatment, and two times on Day 2. No response of the parasitemia was noted and all animals died of malaria.

Tissues from treated monkeys and controls were obtained for election microscope studies by Dr. Carter Atkinson, Case Western Reserve University, Cleveland, Ohio.

ASSESSMENT OF THE ANTIMALARIAL ACTIVITY OF WR 079520AB (BN: BK 70813) AGAINST INFECTIONS OF THE UGANDA PALO ALTO STRAIN OF PLASMODIUM FALCIPARUM

WR 079520, desferrioxamine, is an iron specific chelating agent. Studies at other laboratories have shown that this agent will inhibit, in vitro, the growth of P. falciparum. The in vivo evaluation of desferrioxamine against infections of the Uganda Palo Alto strain was done in collaboration with Dr. Simeon Pollack, Albert Einstein College of Medicine, Bronx, N. Y.

Desferrioxamine was administered by osmotic pumps, implanted subcutaneously, or injected subcutaneously. The results of three experiments are summarized as follows:

1. Implantation of one osmotic pump, containing 400 mg of desferrioxamine, suppressed the parasitemia in 4 of 5 Aotus.

2. Parasitemia was suppressed in 2 of 2 monkeys that were implanted each with two osmotic pumps (a total of 800 mg of desferrioxamine).

3. Insertion of a new pump, on day 8 after the first implantation, had no effect upon parasite multiplication and 2 of 2 Aotus died of malaria.

4. Subcutaneous injection, alone, of desferrioxamine, had no effect upon parasitemia in each of two monkeys.

5. Desferrioxamine, when injected subcutaneously plus implantation of one osmotic pump, cleared parasitemia in 1 of 2 Aotus. The infection, however, was not cured.

The in vitro antimalarial activity of desferioxamine was not confirmed in vivo against infections of a virulent strain of P. falciparum.

ASSESSMENT OF THE ANTIMALARIAL ACTIVITY OF WR 250547AA (BN: BK 51630) AGAINST BLOOD-INDUCED INFECTIONS OF THE NEW GUINEA-CHESSON STRAIN OF PLASMODIUM VIVAX

This stereoisomer of floxacrine was evaluated against trophozoite-induced infections of P. vivax. A dose of 1.0 mg base per kg (x 3 days) cured 1 of 4 infections in Aotus. A dose of 4.0 mg base per kg (x 3 days) cured 6 of 6 infections, and a dose of 16.0 mg base per kg (x 3 days) cured 3 of 4 primary infections. An infection that did not respond to the latter dose was cured with a dose of 64.0 mg base per kg (x 3 days).

A previous evaluation of WR 250547 against infections of the multi-drug resistant Vietnam Smith strain of P. falciparum showed that the drug cured these infections at a dose of either 4.0 or 16.0 mg base per kg (x 3 days). The antimalarial activity of this acridinol against P. vivax was essentially identical.

ASSESSMENT OF THE ANTIMALARIAL ACTIVITY OF WR 250547AA (BN: BK 51630) AND WR 250548AA (BN: BK 51621), IN COMBINATION, AGAINST INFECTIONS OF THE VIETNAM SMITH STRAIN OF PLASMODIUM FALCIPARUM

Both of these acridinol compounds are stereoisomers of floxacrine. Results of the evaluation of each drug, singly, against infections of the multi-drug resistant Vietnam Smith strain indicated that WR 250547 cured primary infections when administered at a dose of 1.0, 4.0 or 16.0 mg base per kg (x 3 days), but WR 250548, administered at these doses, did not cure primary infections.

Evaluation, at other laboratories, of WR 250547 in combination with WR 250548 showed that a potentiating effect was obtained in vitro against P. falciparum and in vivo against P. berghei. These observations provided an impetus to re-evaluate the combination of the two stereoisomers against Vietnam Smith infections in Aotus.

Doses of 0.5 mg base per kg (x 3 days) each of WR 250547 and WR 250548 only cleared parasitemia, and re-treatment with the drugs each at a dose of 1.0 mg base per kg (x 3 days) cured the recrudescence, in addition to a primary infection.

Primary infections were cured by the combined administration of the two drugs at doses of mg base per kg (x 3 days) as follows:

1. WR 250547 (1.0) plus WR 250548 (4.0)

2. WR 250547 (2.0) plus WR 250548 (0.5)

3) WR 250547 (4.0) plus WR 250548 (1.0)

The potentiating antimalarial activity of the two stereoisomers, observed initially in the P. berghei rodent model was confirmed in the P. falciparum - Aotus model. Other experimental antimalarial agents may be evaluated in combination in future trials.

ASSESSMENT OF THE ANTIMALARIAL ACTIVITY OF THREE 9-PHENANTHRENEMETHANOLS AGAINST INFECTIONS OF THE VIETNAM SMITH STRAIN OF PLASMODIUM FALCIPARUM

Two drugs, WR 171669 (halofantrine) and WR 122455, in a series of 9-phenanthrenemethanols, were highly active against chloroquine-sensitive and -resistant strains of P. falciparum in owl monkeys.[1] Evaluation of these two agents in human volunteers infected with the multi-drug resistant strain of P. falciparum showed that while both drugs cured such infections, both evoked gastrointestinal symptoms.[2]

Data from another laboratory indicated that the biquinate salt of halofantrine might enhance the bioavailability of this drug. Both halofantrine, its biquinate salt, and WR 122455 were assessed against Vietnam Smith infections in Aotus.

The chloride salt of halofantrine (WR 171669AM; BN: BK 64002) administered at dose of 2.9, 5.8, or 11.7 mg base per kg (x 3 days) had no effect upon primary parasitemias. Treatment failures were treated with higher doses; cure was obtained in 2 of 22 treatment trials.

Evaluation of the biquinate salt of halofantrine (WR 171669AP; BN: BL 08009) showed that primary Vietnam Smith parasitemias did not respond to doses of 2.9, 5.8, or 11.7 mg base per kg (x 3 days). In a total of 21 treatment trials, the infection in one monkey was cured by a dose of 46.6 mg base per kg (x 3 days).

WR 122455AF (BN: AX26839), at a dose of 2.9 mg base per kg (x 3 days) suppressed primary parasitemia in 2 of 2 Aotus, cured the primary infection in 1 of 2 Aotus when administered at a dose of 5.8 mg base per kg (x 3 days), and at a dose of 11.7 mg base per kg (x 3 days) cured the primary infection in 2 of 2 Aotus. All recrudescent parasitemias, after multiple re-treatment with either WR 171669AM or WR 171669AP were cured by treatment with WR 122455 at doses lower than those of halofantrine or the biquinate salt that did not cure.

At the doses used, both WR 171669AM and its biquinate salt (WR 171669AP) were essentially inactive against Vietnam Smith strain infections. In contrast, WR 122455, in a total of 19 treatments, cured 15 infections, and cured all treatment failures of WR 171669AM and WR 171669AP.

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2. Rinehart, J., Arnold, J. and Canfield, C. 1976. Evaluation of two phenanthrenemethanols for antimalarial activity in man: WR 122455 and WR 171669. Am. J. Trop. Med. Hyg. 25: 769-744.

PILOT EVALUATION OF SODIUM ARTESUNATE AGAINST INFECTION OF THE UGANDA PALO ALTO STRAIN OF *PLASMODIUM FALCIPARUM*

The herb, *Artemisia annua*, has been used in China for more than 1,000 years as a treatment for malaria and fevers. An isolate of this herb, Qinghaosu (QHS, artemisinin), has been successful in the treatment of drug sensitive/resistant strain infections of *P. falciparum* in man. Sodium artesunate, a water soluble derivative of QHS, was more active than QHS against chloroquine-sensitive and chloroquine-resistant strains of *P. berghei* in the rodent model. Additionally, sodium artesunate has been effective in cases of human cerebral malaria. There has been no systematic evaluation of sodium artesunate in the *P. falciparum* - *Aotus* model. Because of the restricted availability of the drug, only one infected *Actus* was used in this pilot study.

A dose of 30.0 mg per kg (x 2), administered intravenously, suppressed parasitemia of the Uganda Palo Alto strain during day 2 through 6 post treatment. Parasitemia then increased to pre-treatment level, and cleared on day 18 after the first day of treatment.

This very limited evaluation indicated some suppressive activity of a *P. falciparum* infection in *Aotus*. Additional trials are dependant upon future availability of drug.

ADAPTATION TRIALS IN *AOTUS* OF THE UNC-W2-MEF CLONE OF *PLASMODIUM FALCIPARUM*

The CDC Indochina III strain of *P. falciparum* is resistant to Fansidar and chloroquine. A clone, UNC-W2, of this strain was made resistant(at another laboratory) to mefloquine during two years of continuous mefloquine pressure *in vitro*. The UNC-W2-MEF clone is 4x more resistant to mefloquine than the parent clone. A culture of this clone was provided by MAJ W.K. Milhous, Walter Reed Army Institute of Research, for adaptation trials to *Aotus*.

Two splenectomized *Aotus*, one of Colombian origin and one from Panama, were each inoculated with 100×10^6 parasites derived from the culture. A patent infection was established in the Colombian monkey, but not in the Panamanian *Aotus*. Parasites from the Colombian *Aotus* were used for re-inoculation of the original Panamanian *Aotus*, a second splenectomized Panamanian *Aotus*, and a normal hybrid *Aotus* (Panamanian x Colombian). To date only moderate infections as indicated by maximum parasitemias have been noted: 60,000 per mm^3 in the Colombian *Aotus*, and 500 per mm^3 in each of the two splenectomized Panamanian *Aotus*. Additional trials are in progress.

LIST OF PERSONNEL WHO RECEIVED SUPPORT UNDER CONTRACT

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